Incidence of IDDM in the Marche Region, Italy

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OBJECTIVE — To provide reliable data concerning the incidence of insulin-dependent diabetes mellitus (IDDM) in children from the Marche Region in Italy and contribute to a better understanding of its geographical variability throughout Italy and Europe.

RESEARCH DESIGN AND METHODS — All newly diagnosed cases of IDDM in children 0–14 years of age in the Marche Region between 1 January 1990 and 31 December 1992 were recorded. The primary source of ascertainment was clinical records from the 59 hospitals of the region. Secondary and tertiary independent sources included local and national associations for diabetic children and local district centers of the National Health System.

RESULTS — Over the 3-year study period, the overall IDDM incidence rate was 8.1 per 100,000/year. No significant sex-related difference in incidence was noted, with a male:female ratio of 0.9. The completeness of ascertainment was estimated at 100%.

CONCLUSIONS — The Marche Region appears to have a slightly elevated incidence of IDDM among noninsular Italian regions.

Insulin-dependent diabetes mellitus (IDDM) is one of the major chronic diseases in childhood and is associated with a range of long-term complications and a poor prognosis (1). In Europe, pronounced geographical variations in incidence have been noted (2–7); however, until the Eurodiab Subarea A Report, little information on IDDM incidence in southern Europe was available (8). Incidence data for all Italian regions are not yet available, although IDDM risk appears to vary widely (8–10), with an extremely high incidence in Sardinia (11). There have been no previous reports of the incidence of IDDM in the Marche Region.

Situated on the east coast of the Italian peninsula, the Marche Region covers an area of 9,693 km^2 and has a population of 1,453,574 (12). The region is divided into four provinces—Pesaro, Ancona, Macerata, and Ascoli Piceno—that have only slight variations in population density and dietetic habits but notable differences in speech (13). The aim of our study was to organize a population-based IDDM registry for the pediatric population of the Marche Region and to provide reliable data on the incidence of the disease that contributes to a better understanding of its epidemiology and geographical variability throughout Italy and among countries in the Mediterranean area. In this study, we report the incidence rate of IDDM among children of the Marche Region who were 0–14 years of age and diagnosed between 1 January 1990 and 31 December 1992.

RESEARCH DESIGN AND METHODS

— The 1991 estimates of the Italian Central Institute for Statistics (ISTAT) provided the necessary information on the population size for the Marche Region. The total population consists of 1,435,574 inhabitants, with 206,601 in the 0–14 age-group: 105,989 are men and 100,612 are women. The populations at risk (those 0–14 years of age) in each of the four provinces of the region are: 48,562 in Pesaro; 63,165 in Ancona; 42,746 in Macerata; and 52,128 in Ascoli Piceno (12). The criteria for diagnosis of IDDM were those established by the World Health Organization Diamond Project Group (15): *1*) diagnosed with diabetes, 2) <15 years of age at first insulin administration, and *3*) resident of the study area at the time of diagnosis. All newly diagnosed IDDM cases occurring between 1 January 1990 and 31 December 1992 were recorded. The date of diagnosis was equated with the date of the first insulin injection according to international recommendations (14). The following data, taken from clinical files, were recorded for each patient: name, sex, ethnic group, date of birth, address at birth and at diagnosis, date of first insulin administration, family history of diabetes (IDDM or NIDDM) or other diseases, past history of vaccination, height and weight at diagnosis, and laboratory data at admission (including ketosis and blood glucose concentration at diagnosis). Using

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IDDM, insulin-dependent diabetes mellitus; CI, confidence interval; ISTAT, Italian Central Institute for Statistics; AFAID, Associazione delle Famiglie con Adolescenti o Infanti Diabetici.

Table 1—*Incidence rate of IDDM in the Marche Region during 1990–1992*

	Population size	Observed cases (*n*)	Incidence rate (per 100,000/year)	CI
Men				
Age-groups (years)				
0–4	31,014	4	4.3	1.2–11.0
5–9	33,726	11	10.9	5.4–19.5
10–14	41,249	10	8.1	3.9–14.8
Age range (years)				
0–14	105,989	25	7.9	5.1–11.6
Women				
Age-groups (years)				
0–4	29,377	4	4.5	1.2–11.6
5–9	32,085	11	11.4	5.7–20.5
10–14	39,150	10	8.5	4.1–15.7
Age range (years)				
0–14	100,612	25	8.3	5.4–12.3
Both sexes				
Age-groups (years)				
0–4	60,391	8	4.4	1.9–8.7
5–9	65,811	22	11.2	7.0–16.8
10–14	80,399	20	8.3	5.1–12.8
Age range (years)				
0–14	206,601	50	8.1	6.0–10.6
Age-standardized rate				
0–14			7.9	5.9–10.4

clinical and laboratory data, cases of secondary diabetes and maturity-onset diabetes of the young were excluded. The clinical records from the 59 hospitals in the Marche region (including divisions of medicine, pediatrics, and endocrinology, university departments, and diabetic centers for adult patients) were used as the primary source of ascertainment. As a secondary and independent source, we used the local district centers of the National Health System, where syringes, blood glucose monitoring strips, and insulin are distributed free of charge; as a tertiary independent source, we referred to the local and national IDDM associations for children (Associazione delle Famiglie con Adolescenti o Infanti Diabetici [AFAID] and Federazione Nazionale Diabete Giovanile). We calculated age- and sex-specific incidence rates as previously described (8). For comparison purposes, age-standardized rates were calculated for each sex and for the total population (16). The standard population assumes equal numbers in each of the age-groups 0–4, 5–9, and 10–14 for each sex. The completeness of ascertainment was based on the capture-recapture model (17). The 95% confidence intervals (CIs) were estimated using a Poisson distribution (18). The χ^2 test was used to test the significance of differences between incidence data. The seasonal variation was evaluated according to the method described by Roger (19).

RESULTS — The combined case ascertainment from primary, secondary, and tertiary sources was 100%. All cases recorded from the primary source were also identified by the secondary source. The tertiary source identified 21 of 50 cases, all of which were also recognized by the primary and secondary sources. We observed 50 diabetic children over the 3-year period: 16 from 1990 (7.5 per 100,000; 95% CI 4.3–12.2), 19 from 1991 (9.0 per 100,000; CI 5.4–14.0), and 15 from 1992 (7.1 per 100,000; CI 4.0–11.7). The average annual incidence rate for individuals aged 0–14 years was 8.1 per 100,000/year. The highest incidence rate (11.2 per 100,000/year) was seen for the 5–9 year age-group; for the 0–4 year age-group the rate was 4.4 per 100,000/year; and for the 10–14 year age-group 8.3 per 100,000/year (Table 1). No significant differences (by χ^2 test) between sexes were noted, with a male:female ratio of 0.9. Age-specific incidence rates and corresponding CI by province are shown in Fig. 1. The intraregional variation, with rates ranging from 6.2 to 10.9, was not found to be significant by χ^2 test. Analysis of the diagnosis month ($R = 0.29$) revealed a slight but nonsignificant increase in newly diagnosed children during the cold months (October-February).

CONCLUSIONS — This report represents the first validated study of IDDM incidence in the pediatric population of the Marche Region in Italy. It reveals a crude incidence rate of 8.1 per 100,000/year (95% CI 6.0–10.6) for children <15 years of age during 1990–1992. All patients identified from the primary source (clinical records) were also recognized by the secondary source (local districts of the National Health System); the tertiary source (diabetic associations) was less useful. The excellent ascertainment capacity of the primary (100%) and secondary (100%) sources may reflect a homogeneous distribution of the hospitals throughout the region, as well as considerable cooperation between pediatricians and diabetologists. The low ascertaiment rate from the diabetic associations (42%) is probably because AFAID was only founded in 1988. The age-standardized incidence rate of the Marche Region (Table 1) did not differ significantly from other areas within the Italian peninsula. It was slightly higher than that of other regions of central Italy, including Lazio (6.8 per 100,000/year; 95% CI 5.4–7.8) (8)

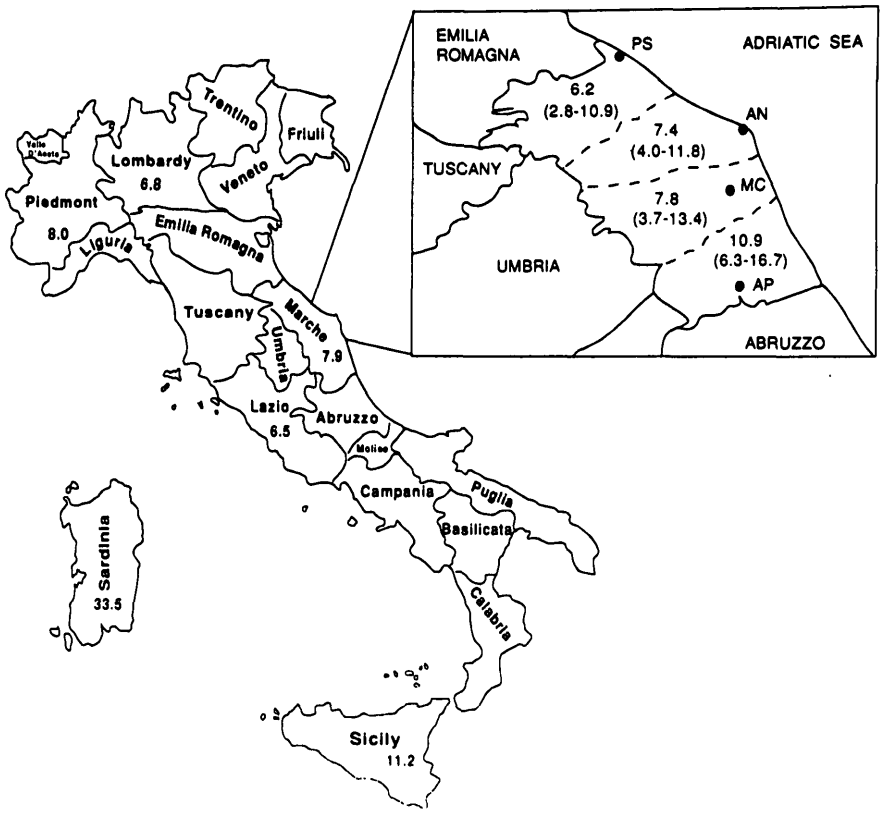

Figure 1—*Incidence rates of IDDM in Italy by region. Age-standardized incidence rates (per 100,000/year, onset 0–14 years) are reported for a whole region when available, except for Sicily (data from east Sicily only). The Marche Region age-specific 0–14 year incidence rates (per 100,000/year) and CI (in brackets) are reported by province: PS, Pesaro; AN, Ancona; M, Macerata; AP, Ascoli Piceno.*

and Lombardy (6.8 per 100,000/year; 95% CI 5.8–7.8) in Northern Italy (8). For corresponding age-groups, the incidence of IDDM in the Marche Region appears to be similar to that of the Piedmont Region (8.0 per 100,000/year; 95% CI 5.8–10.9) (8). In contrast, a child born in Sardinia has almost a four-times greater risk of IDDM than a child born in Marche (11). We observed the highest incidence rates for children in the 5–9 year age-group, regardless of sex. Other regions of Italy have reported similar patterns, but, throughout Europe, the peak incidence has appeared in the 10–14 year age-group (8). This peak suggests genetic differences or exposure to environmental agents in younger Italian children. The seasonal pattern observed in other Mediterranean countries matched the increased number of cases diagnosed in the Marche during the winter months (7). Moreover, a slight variation in incidence was found within the region between north and south provinces (Fig. 1). This difference may become significant with continued follow-up. It should be noted that linguistic differences exist between the north and the south provinces, reflecting possible genetic variation within the region (13). In conclusion, the Marche Region has a slightly higher incidence of IDDM cases than other noninsular regions of Italy. The slight geographic variation, possibly because of genetic heterogeneity within the region, requires further evaluation using molecular epidemiological approaches and continued follow-up to determine its significance. Investigation is continuing to collect data on environmental factors, including breast-feeding and other nutritional variables across the Marche Region.

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References

1. Alberti KGMM, De Fronzo RA, Zimmet P: *International Textbook of Diabetes Mellitus*. New York, Wiley, 1992
2. Diabetes Epidemiology Research International Group: Geographic pattern of childhood insulin-dependent diabetes. *Diabetes* 37:1113–1119, 1990
3. Tuomiletho J, Podar T, Reunanen A, Kal-

its I, Lounamaa R, Tuomiletho-Wolf E, Adojaan B, Neff B, LaPorte RE: Comparison of incidence of IDDM in children between Estonia and Finland, 1980–1988. *Diabetes Care* 14:982–988, 1991

4. Green A, Andersen PK, Svendsen AJ, Mortensen K: Increasing incidence of early onset type I (insulin-dependent) diabetes mellitus: a study of Danish male birth cohorts. *Diabetologia* 35:178–182, 1992
5. Drykoningen EM, Mulder ALM, Vaandrager GJ, LaPorte RE, Bruining GJ: The incidence of male childhood type I (insulin-dependent) diabetes mellitus is rising in the Netherlands. *Diabetologia* 35:139–142, 1992
6. Levy-Marchal C, Papoz L, Beaufort C, Doutreix J, Froment V, Voirin J, Collignon A, Garros B, Schlerety Y, Czernichov P: Incidence in juvenile type I (insulin-dependent) diabetes in France. *Diabetologia* 33:465–469, 1990
7. Goday A, Castell C, Tresserras R, Canela J, Taberner JL, Lioveras G, Catalan Epidemiology Diabetes Study Group: Incidence of type I (insulin-dependent) diabetes mellitus in Catalonia, Spain. *Diabetologia* 35:267–271, 1992
8. Green A, Gale EAM, Patterson CC, the Eurodiab Ace Study Group: Incidence of childhood-onset insulin-dependent diabetes mellitus: the Eurodiab Ace Study Group. *Lancet* 339:905–909, 1992
9. Bruno G, Merletti F, Pisu E, Pastore G, Marengo C, Pagano G: Incidence of IDDM during 1984–1986 in population aged <30 yr: residents of Turin, Italy. *Diabetes Care* 13:1051–1056, 1990
10. Deri Study Group: The epidemiology and immunogenetics of IDDM in Italian heritage populations. *Diabetes Metab Rev* 6:63–69, 1990
11. Muntoni S, Songini M, Sardinian Collaborative Group for Epidemiology of Diabetes: High incidence rate of IDDM in Sardinia. *Diabetes Care* 15:1317–1322, 1992
12. *Istituto Centrale di Statistica: Popolazione e movimento anagrafico nei singoli comuni delle Marche*. Rome, Italy, ISTAT, *1991, p. 190–191*
13. Parrino F: Presupposti etnici e linguistici della frammentazione linguistica nelle Marche. In *Studi Maceratesi*. Vol. 9. Macerata, Italy, Tipografia Maceratese, 1975, p. 341–354
14. World Health Organization Diamond Project Group: WHO multinational project for childhood diabetes. *Diabetes Care* 13:1062–1068, 1990
15. LaPorte RE, Tajima N, Akerblom HR, Berlin R, Brosseau J, Christy M, Drash AL, Fishbein H, Green A, Hamman R, Harris M, King H, Laron Z, Neil A: Geographic differences in the risk of insulin-dependent diabetes mellitus: the importance of registries. *Diabetes Care* 8 (Suppl. 1):101–107, 1985
16. Rothman KJ: *Modern Epidemiology*. Boston, Little, Brown, 1986, p.41–44
17. Bishop YMM, Fiemberg SE, Holland PV: *Discrete Multivariate Analysis: Theory and Practice*. Cambridge, MA, MIT Press, 1974
18. Hazard Munro B, Visintainer MA, Page EB: *Statistical Methods for Health Care Research*. Philadelphia, PA, Lippincott, 1986
19. Roger JH: A significance test for cyclic trends in incidence data. *Biometrika* 64: 152–155, 1977